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Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a randomised head-to-head study

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ABSTRACT

Objective To directly compare the efficacy of natalizumab and fingolimod in patients with active relapsing-remitting multiple sclerosis.

Methods This phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study was conducted at 43 sites in nine countries. Patients were randomised (1:1) to intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once daily for ≤52 weeks. Enrolment-related early study termination precluded assessment of the primary endpoint (evolution of new on-treatment gadolinium-enhancing [Gd+] lesions to persistent black holes). Consistent with secondary objectives, exploratory analyses were conducted of treatment effects on new T1 Gd+ lesions, new/newly enlarging T2 lesions and relapses.

Results The intent-to-treat population comprised 108 patients (natalizumab, n=54; fingolimod, n=54); 63 completed ≥24 weeks of treatment. Due to the limited numbers of events and patients at risk, MRI and relapse outcomes were reported over up to 24 and 36 weeks, respectively. The mean number of new T1 Gd+ lesions was numerically lower with natalizumab than with fingolimod by 4 weeks; accumulation rates were 0.02 and 0.09 per week, respectively, over 24 weeks (p=0.004). The cumulative probability of developing ≥1 lesion at 24 weeks was 40.7% with natalizumab versus 58.0% with fingolimod (HR=1.66; 95% CI 0.87 to 3.26; p=0.126); the corresponding probabilities for ≥2 lesions were 11.5% versus 48.5% (HR=4.05; 95% CI 1.47 to 11.14; p=0.007). No significant between-group differences were observed for the other MRI outcomes at 24 weeks. The cumulative probability of relapse over follow-up was 1.9% with natalizumab

versus 22.3% with fingolimod (HR=12.18; 95% CI 1.55 to 95.63; p=0.017). Adverse events were consistent with known safety profiles.

Conclusions These results suggest that natalizumab is more efficacious than fingolimod in reducing multiple sclerosis relapses and T1 Gd+ lesion accumulation in patients with active disease.

Clinicaltrials.gov registration number NCT02342704.

EudraCT registration number EUCTR2013-004622-29-IT.

Strengths and limitations of this study

- This phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study is the first randomised controlled trial to compare the efficacy of natalizumab and fingolimod in patients with relapsing-remitting multiple sclerosis.
- Patients (n=108) were randomised (1:1) to intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once daily for up to 52 weeks.
- The primary endpoint, evolution of new on-treatment gadolinium-enhancing lesions to persistent black holes, could not be assessed due to early study termination.

- Secondary endpoints, including treatment effects on gadolinium-enhancing T1 lesions, T2 lesions and relapse outcomes, were assessed as well as safety findings.
- Secondary endpoints were reported over a relatively short treatment period of 24–36 weeks, precluding assessment of long-term outcomes.

INTRODUCTION

Natalizumab and fingolimod are well-established, efficacious disease-modifying therapies for relapsing-remitting multiple sclerosis (RRMS), demonstrating reductions in clinical and radiological measures of disease activity in pivotal placebo-controlled trials.[1-5] Previous analyses have indicated that both natalizumab and fingolimod exhibit beneficial effects quickly (within 2 months) after treatment initiation,[6-9] which may be an important consideration in treatment selection, especially in patients with active disease. However, evidence regarding the relative efficacy of natalizumab and fingolimod has, to date, been limited to retrospective analyses of registry datasets.[10-12]

This study reports results from REVEAL, a 1-year, randomised, rater- and sponsor-blinded, prospective head-to-head study comparing natalizumab and fingolimod in patients with active RRMS. Although early study closure precluded analysis of the primary efficacy endpoint, available MRI data were used in exploratory analyses of secondary endpoints to directly compare natalizumab versus fingolimod efficacy within 4 weeks of therapy initiation. In addition, relapse data were analysed to assess annualised relapse rates (ARRs) and the cumulative probability of relapse over the duration of the study.

METHODS

REVEAL was a phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study conducted at 43 sites in nine countries between October 2014 and May 2016 (planned overall duration, 68 weeks) in accordance with

the Declaration of Helsinki and Good Clinical Practice Guidelines (clinicaltrials.gov identifier NCT02342704; EudraCT identifier EUCTR2013-004622-29-IT).[13] All sites received institutional review board approval, and all participants provided written informed consent. REVEAL was designed to include approximately 540 patients. However, after 1 year of enrolling patients, only 111 patients had been enrolled. The decision to terminate the study due to slow enrolment was made by the sponsor in November 2015. Outcome data were not made available until May 2016, and all scheduled MRI scans were evaluated in a blinded manner. Thus, the study termination decision was made without knowledge of the results.

Patients were aged 18–60 years and had active RRMS not previously treated with natalizumab, fingolimod or immunosuppressants, with ≥1 new T1 gadolinium-enhancing (Gd+) lesion within the 6 months prior to screening or ≥2 new T2 lesions on brain MRI within the 6 months prior to screening (compared with a T2-weighted scan 18 months before screening) as well as an Expanded Disability Status Scale (EDSS) score ≤5.5. Included patients could have previously been treated for ≥6 months with glatiramer acetate or an interferon beta formulation if they had ≥9 T2-hyperintense lesions on brain MRI and experienced ≥1 relapse while on therapy within the 6 months prior to screening. Multiple sclerosis (MS) treatment–naïve patients and patients who had previously been treated for <6 months with glatiramer acetate or an interferon beta formulation were included only if they had ≥2 disabling relapses within the 12 months prior to screening. Patients with progressive MS were excluded.

Following a 4-week screening period, patients were randomly assigned (1:1) to open-label intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once

daily for up to 52 weeks, then followed for up to 64 weeks. MRI scans were scheduled every 4 weeks for the first 24 weeks and then at 36 and 52 weeks. A follow-up visit approximately 12 weeks after the last dose of study drug was planned.

Relapses and adverse events (AEs) were assessed at scheduled visits. A clinical relapse was defined as new or recurrent neurological symptoms, not associated with fever, lasting for at least 24 hours, and followed by a period of 30 days of stability or improvement. New or recurrent neurological symptoms that occurred fewer than 30 days after the onset of a protocol-defined relapse were considered part of the same relapse. MS relapses were not considered AEs, and MS relapses resulting in hospitalisation did not need to be reported as serious AEs (SAEs). However, any MS relapse that was complicated by other SAEs was reported as an SAE.

The intent-to-treat (ITT) population for efficacy analysis comprised all randomised subjects given ≥1 dose of study drug who provided any efficacy assessments. The primary endpoint (the evolution of new on-treatment T1-weighted Gd+ lesions to persistent black holes over 52 weeks) could not be assessed due to the lack of 52-week data. Secondary endpoints included the number of new T1 Gd+ lesions, the cumulative probability of developing new T1 Gd+ lesions, the number of new/newly enlarging T2 lesions, T1 and T2 lesion volumes and relapse outcomes. MRI and relapse outcomes were assessed over the study duration according to the protocol. However, due to the limited numbers of events and patients at risk, MRI outcomes were reported over up to 24 weeks, while relapse outcomes were reported over up to 36 weeks. Other secondary endpoints, including no evidence of disease activity and change in information processing speed as measured by the Symbol Digit Modalities Test, were not

interpretable due to the early closure of the study. Safety was assessed based on AEs, laboratory measurements, vital signs and physical examinations.

Treatment groups were compared using negative binomial regression models, and Cox regression models were developed for probability analyses. P values for comparisons in new T2 lesions and lesion volume changes were determined using a Wilcoxon rank-sum test.

A diffusion tensor imaging substudy including healthy volunteers was conducted to assess brain tissue damage and recovery in patients with active RRMS. Due to study termination, results were unevaluable.

Patient involvement

Patients were not involved in the design, conduct, reporting, or dissemination of this research.

RESULTS

The ITT population (table 1) comprised 108 patients (online supplementary figure 1); 63 patients (58.3%; natalizumab, n=32; fingolimod, n=31) received study treatment through 24 weeks, whereas only 3 (2.8%; natalizumab, n=2; fingolimod, n=1) were treated through 52 weeks (table 2). Median (range) follow-up time was 40.1 (7.1–64.7) weeks for natalizumab and 36.7 (7.0–64.1) weeks for fingolimod.

Table 1 Baseline demographics and characteristics

Characteristic	Natalizumab (n=54)	Fingolimod (n=54)
Age, years		
Mean (SD)	38.2 (8.81)	34.9 (8.73)
Median (min, max)	40 (21, 55)	35 (19, 55)
Sex, n (%) female	37 (68.5)	38 (70.4)
EDSS score		
Mean (SD)	2.5 (1.31)	2.6 (1.33)
Median (min, max)	2.0 (0.0, 6.0)	2.5 (0.0, 5.5)
Time since first MS symptoms, mean (SD), years	8.1 (7.72)	6.8 (6.98)
Time since MS diagnosis, mean (SD), years	5.0 (5.80)	4.5 (5.75)
Prior MS treatment, n (%) of patients*	26 (48.1)	28 (51.9)
Time since most recent relapse, mean (SD), days	86.8 (58.78)	91.2 (91.40)
Number of relapses in the past year, mean (SD)	1.9 (0.65)	1.9 (0.62)
Number of Gd+ lesions		
Mean (SD)	2.4 (3.65)	2.5 (4.94)
Median (min, max)	1 (0, 14)	1 (0, 28)
T2 lesion volume, mL		
Mean (SD)	11.9 (9.42)	10.9 (10.36)
Median (min, max)	8.5 (0.7, 40.1)	7.7 (0.1, 43.2)
T1-nonenhancing lesion volume, mL		
Mean (SD)	2.3 (2.37)	2.4 (3.36)
Median (min, max)	1.3 (0, 8.6)	1.1 (0, 15.3)

*Most commonly glatiramer acetate (natalizumab, n=7; fingolimod, n=9) and interferon beta (subcutaneous [SC] interferon beta-1a: natalizumab, n=10; fingolimod, n=6; intramuscular interferon beta-1a: natalizumab, n=4; fingolimod, n=10; SC interferon beta-1b: natalizumab, n=1, fingolimod, n=5; SC interferon beta-1b: natalizumab, n=1, fingolimod, n=2).

EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhanced; max, maximum; min, minimum; MS, multiple sclerosis; SD, standard deviation.

Table 2 Treatment exposure and safety outcomes

	Natalizumab (n=54)	Fingolimod (n=54)
Study drug exposure, days		
Mean (SD)	183.0 (90.9)	182.6 (101.8)
Median (range)	197 (1–364)	172 (1–362)
Patients receiving treatment at each time point, n (%)		
Baseline	54 (100)	54 (100)
Week 4	52 (96.3)	50 (92.6)
Week 8	50 (92.6)	47 (87.0)
Week 12	45 (83.3)	45 (83.3)
Week 16	42 (77.8)	40 (74.1)
Week 20	36 (66.7)	35 (64.8)
Week 24	32 (59.3)	31 (57.4)
Week 32	25 (46.3)	23 (42.6)
Week 40	11 (20.4)	13 (24.1)
Week 52	2 (3.7)	1 (1.9)
Treatment-emergent adverse events, n (%) of patients	23 (42.6)	32 (59.3)
Most commonly reported events, n (%) of patients*		
Headache	6 (11.1)	4 (7.4)
MS relapse	1 (1.9)	8 (14.8)
Hypoesthesia	0	3 (5.6)
Migraine	0	3 (5.6)
Upper respiratory tract infection	1 (1.9)	5 (9.3)
Urinary tract infection	2 (3.7)	3 (5.6)
Lymphocyte count decreased	0	5 (9.3)
Alanine aminotransferase increased	0	3 (5.6)
Anxiety	1 (1.9)	3 (5.6)
Fatigue	3 (5.6)	0
Oropharyngeal pain	3 (5.6)	1 (1.9)
Serious adverse events, n (%) of patients	0	2 (3.7)
Second-degree atrioventricular block	0	1 (1.9)
Migraine with aura	0	1 (1.9)
Events leading to study discontinuation, n (%) of patients†	1 (1.9)	3 (5.6)
Second-degree atrioventricular block	0	1 (1.9)
Infusion site rash	1 (1.9)	0
Alanine aminotransferase increased	0	1 (1.9)
Aspartate aminotransferase increased	0	1 (1.9)
Headache	0	1 (1.9)
Patients who discontinued, n (%)	53 (98.1)‡	51 (94.4)§

*Treatment-emergent adverse events reported by ≥5% patients in either group, listed by MedDRA preferred term.
†With the exception of atrioventricular block, adverse events leading to study discontinuation were classified as non-serious events.
‡Forty-nine patients discontinued due to sponsor study termination, two were lost to follow-up, one discontinued due to an AE and one discontinued due to withdrawal of consent.
§Forty-three patients discontinued due to sponsor study termination, three discontinued due to AEs, three discontinued due to physician decision, one was lost to follow-up and one discontinued for another reason.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; SD, standard deviation.

The mean number of new T1 Gd+ lesions was 63% lower in the natalizumab group than the fingolimod group at 4 weeks (p=0.353) and ≥70% lower at 12 weeks (p=0.030; figure 1), a difference that was maintained (with reduced patient numbers) through 24 weeks (p=0.008). Over 24 weeks, new T1 Gd+ lesion accumulation was lower among natalizumab- than fingolimod-treated patients (0.02 vs 0.09 new lesions per week; p=0.004). Over the entire follow-up period, natalizumab-treated patients were significantly less likely than fingolimod-treated patients to develop ≥2 or ≥3 new T1 Gd+ lesions (table 3). No significant between-group differences were observed in other MRI outcomes at 24 weeks; however, all MRI results numerically favoured natalizumab (table 3).

Table 3 Key MRI and clinical outcomes

Outcomes	Natalizumab (n=54)	Fingolimod (n=54)	HR (95% CI)	p value*
MRI outcomes: T1 Gd+ lesions				
Cumulative probability of developing new T1 Gd+ lesions over study, %				
≥1	40.68	57.99	1.66 (0.87 to 3.26)	0.126
≥2	11.54	48.48	4.05 (1.47 to 11.14)	0.007
≥3	10.02	41.38	4.09 (1.30 to 12.89)	0.016
Number of patients with new T1 Gd+ lesions from baseline to 24 weeks, n/N (%)	16/47 (34.0)†	24/45 (53.3)†	NA	0.062
Change from baseline in T1 Gd+ lesion volume to 24 weeks, mean (SD)	0.5 (31.24)‡	1.8 (19.70)‡	NA	0.532
MRI outcomes: T2 lesions				
Number of patients with new/newly enlarging T2 lesions at 24 weeks, n/N (%)	6/15 (40.0)	10/16 (62.5)	NA	0.210
Number of new/newly enlarging T2 lesions at 24 weeks per patient, mean (SD)	1.33 (2.469)‡	1.94 (2.205)‡	NA	0.263
Change from baseline in T2 lesion volume to 24 weeks, mean (SD)	0.1 (4.40)‡	3.3 (5.04)‡	NA	0.053
Relapse outcomes				
Cumulative probability of relapse over study, %§	1.9	22.3	12.18 (1.55 to 95.63)¶	0.017
ARR on study (95% CI)	0.05 (0.01 to 0.20)	0.29 (0.16 to 0.53)	NA	0.023**

*p value based on a Cox model adjusted for the baseline number of Gd+ lesions, age, baseline EDSS score and years since first symptom (for the cumulative probability of new T1 Gd+ lesions during follow-up), from a chi-square test between the two treatment groups (for the number of patients with new lesions) or based on a Wilcoxon rank-sum test between the two treatment groups (for the number of new/newly enlarging T2 lesions and changes in lesion volume).
†Includes patients with new T1 Gd+ lesions at any time point after baseline. Not all patients received treatment through 24 weeks.
‡Natalizumab, n=15; fingolimod, n=16. Includes only patients who had MRI data through 24 weeks.
§Cumulative probabilities at 36 weeks are reported, as no relapse events were observed after 36 weeks.
¶Based on Cox model adjusted for the number of relapses in the year before baseline, age, baseline EDSS score and years since first symptom.
**p value based on a negative binomial model of ARR with treatment as effect, adjusted for the number of relapses in the year before baseline, baseline EDSS score and baseline age, with log of year on study as offset.
ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MS, multiple sclerosis; NA, not applicable.

During follow-up in this abbreviated study, natalizumab-treated patients were significantly less likely than fingolimod-treated patients to experience a relapse (table 3). The cumulative probability of relapse over follow-up was 1.9% with natalizumab and 22.3% with fingolimod (HR=12.18; 95% CI 1.55 to 95.63; p=0.017; figure 2A). Pre-treatment annualised relapse rates in the natalizumab and fingolimod treatment groups were 1.91 and 1.87, respectively (figure 2B). The on-treatment ARR was 0.05 in the natalizumab group (a 97.4% reduction) and 0.29 in the fingolimod group (an 84.5% reduction). The on-treatment ARR was 83% lower with natalizumab than with fingolimod (p=0.023).

Treatment-emergent AEs were reported for 42.6% and 59.3% of natalizumab- and fingolimod-treated patients, respectively, including two serious AEs, both in patients on fingolimod (table 2). All safety findings were consistent with the known safety profiles for natalizumab and fingolimod.[14,15]

DISCUSSION

These exploratory analyses of REVEAL secondary endpoints indicate that natalizumab reduces T1 Gd+ lesion accumulation and relapse disease activity soon after initiation, consistent with previous clinical trial findings.[6,7] Treatment effects on MRI outcomes were observed within 4 weeks of starting natalizumab.

While both treatments were efficacious in patients with active RRMS, reduction in disease activity, measured by the number of new T1 Gd+ lesions and relapses, occurred more rapidly and to a greater extent with natalizumab than with fingolimod.

These results extend previous findings of the efficacy advantage of natalizumab over fingolimod in preventing relapses and reducing disease activity from comparative analyses of patients with active RRMS or prior treatment failure followed up for 1–2 years in real-world settings.[10-12] No significant between-group differences were observed for other MRI outcomes, such as lesion volume and the number of new/newly enlarging T2 lesions.

Safety findings in this study were consistent with the established profile of each treatment, with no new safety concerns noted.[14,15]

Although REVEAL was designed as a randomised controlled trial, results should be interpreted with caution, as analysis of the primary endpoint was not possible due to early study closure. However, bias in the results due to early study termination is unlikely based on the timing of the decision (before outcome data availability) and the blinding of the sponsor and MRI readers. Secondary efficacy evaluations were limited to a relatively short treatment period of 24–36 weeks, precluding meaningful assessment of EDSS score change. A further limitation is that the long-term consequences of these relatively short-term findings are unknown.

In conclusion, the results suggest greater benefit with natalizumab than with fingolimod in reducing relapse rates and T1 Gd+ lesion accumulation in patients with active RRMS. The onset of efficacy occurred more rapidly with natalizumab than with fingolimod, which may be an important consideration for treatment selection in patients with active disease, who need swift and effective control of disease activity.

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Contributors HB, DJ, DLA, MF, JJGG and P-RH: study design. All authors: analysis and interpretation of data. HB, SL and P-RH: manuscript development. All authors: revising the manuscript for intellectual content.

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Patient consent Obtained.

Ethics approval The study was approved by ethics committees for all participating study centres.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability Datasets from this study are not publicly available. Requests for de-identified data should be made to Biogen via established company data-sharing policies as detailed on the website http://clinicalresearch.biogen.com/.

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FIGURE LEGENDS

Figure 1 Mean cumulative number of new Gd+ lesions on T1-weighted MRI scans reported over 24 weeks. *Reduction is for natalizumab versus fingolimod. P value is based on a negative binomial regression model adjusted for baseline T1 Gd+ lesion count. Gd+, gadolinium enhancing; SEM, standard error of the mean.

Figure 2 Impact of natalizumab versus fingolimod treatment on relapse outcomes, shown as (A) Kaplan-Meier survival curve of time to relapse over 52 weeks and (B) ARRs before study and on study. *Fingolimod versus natalizumab, based on a Cox model adjusted for number of relapses in the year before baseline, age, baseline EDSS score and years since first symptom. †The x-axis has been truncated at week 36, as no events were observed after week 36. ‡p value is based on a negative binomial model of ARR with treatment as effect, adjusted for number of relapses in the year before baseline, baseline EDSS score and baseline age, with log of year on study as offset. ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale.

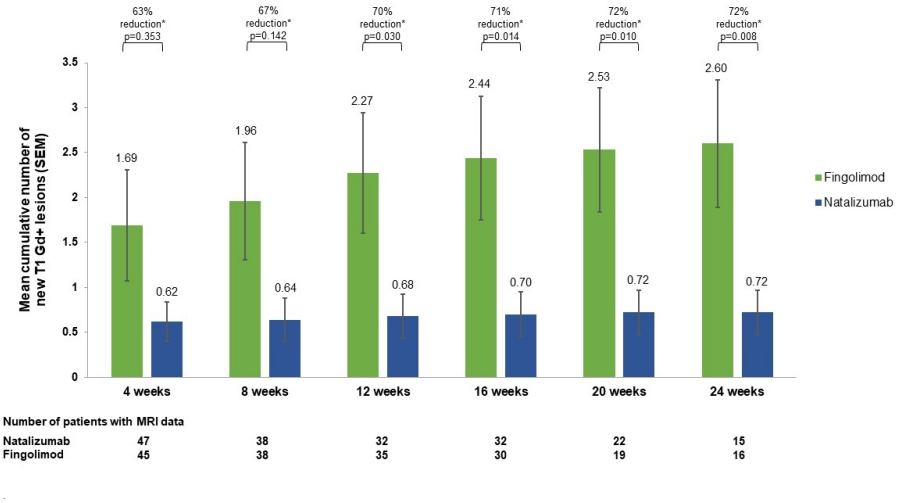

Figure 1 Mean cumulative number of new Gd+ lesions on T1-weighted MRI scans reported over 24 weeks. *Reduction is for natalizumab versus fingolimod. P value is based on a negative binomial regression model adjusted for baseline T1 Gd+ lesion count. Gd+, gadolinium enhancing; SEM, standard error of the mean.

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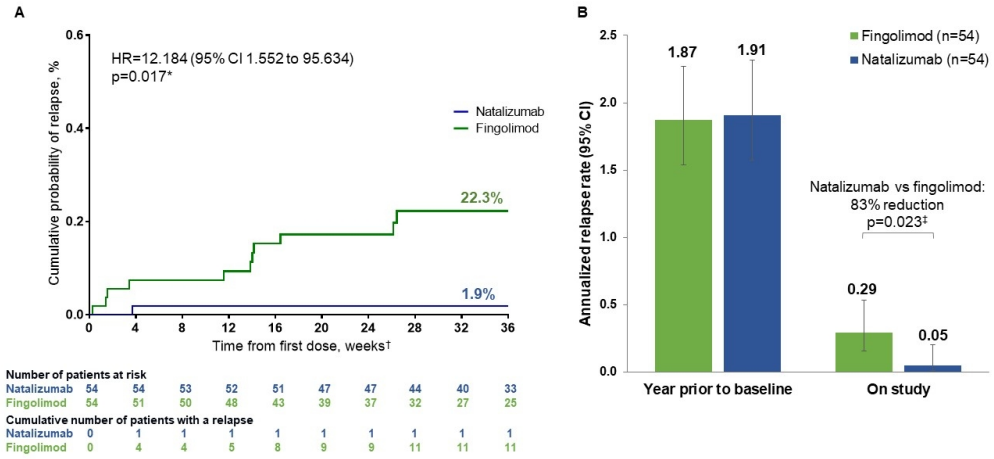
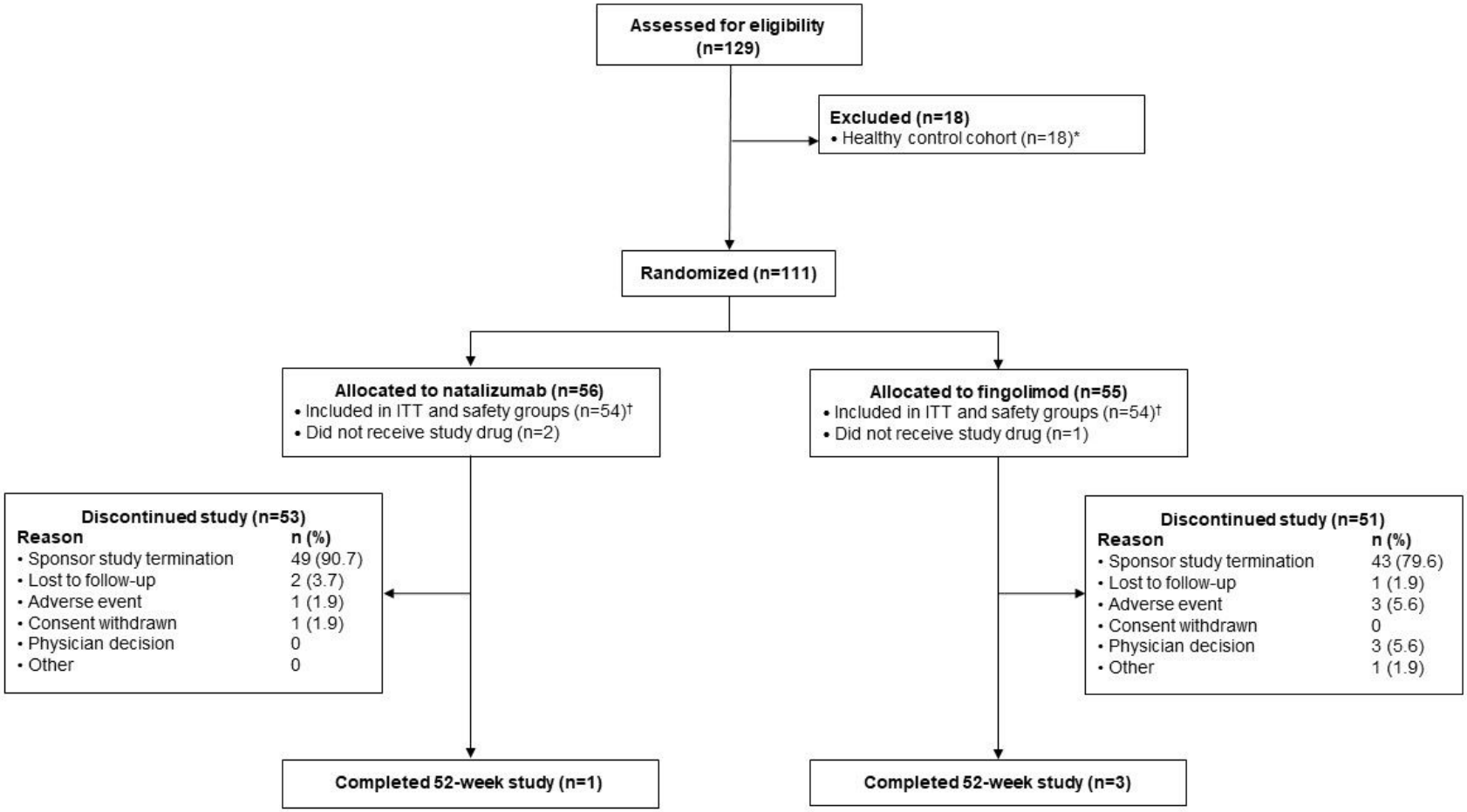


Figure 2 Impact of natalizumab versus fingolimod treatment on relapse outcomes, shown as (A) Kaplan-Meier survival curve of time to relapse over 52 weeks and (B) ARRs before study and on study. *Fingolimod versus natalizumab, based on a Cox model adjusted for number of relapses in the year before baseline, age, baseline EDSS score and years since first symptom. †The x-axis has been truncated at week 36, as no events were observed after week 36. ‡p value is based on a negative binomial model of ARR with treatment as effect, adjusted for number of relapses in the year before baseline, baseline EDSS score and baseline age, with log of year on study as offset. ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale.

338x190mm (96 x 96 DPI)

Online supplementary figure 1 Patient flow



*Healthy control subjects were screened as part of the diffusion tensor imaging substudy being conducted along with the main study in patients with relapsing-remitting multiple sclerosis. These patients were not treated with natalizumab or fingolimod and were not included in the main study results.
†The safety group comprised all randomised patients who received at least one dose of study drug; the ITT group comprised all randomised patients who received at least one dose of study drug and provided at least one efficacy assessment.
ITT, intent-to-treat.

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Arnfin Bergmann	Neurologische Praxis, Germany	Site investigator	Participated in data collection
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Antonio Uccelli	Azienda Ospedaliera Universitaria San Martino, Italy	Site investigator	Participated in data collection
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Jose Meca Lallana	Hospital Universitario Virgen de la Arrixaca, Murcia, Spain	Site investigator	Participated in data collection
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3–4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5–6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5–6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6–7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7–8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7–8
Sample size	7a	How sample size was determined	6, 8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5–6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13–14
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study

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Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study

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ABSTRACT

Objective To directly compare the efficacy of natalizumab and fingolimod in patients with active relapsing-remitting multiple sclerosis.

Methods This phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study was conducted at 43 sites in nine countries. Patients were randomised (1:1) to intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once daily for ≤52 weeks. Enrolment-related early study termination precluded assessment of the primary endpoint (evolution of new on-treatment gadolinium-enhancing [Gd+] lesions to persistent black holes). Unplanned exploratory analyses of secondary endpoints evaluated the effects of treatment on the development of new T1 Gd+ lesions and new/newly enlarging T2 lesions, lesion volumes and relapse outcomes.

Results The intent-to-treat population comprised 108 patients (natalizumab, n=54; fingolimod, n=54); 63 completed ≥24 weeks of treatment. Due to the limited numbers of events and patients at risk, MRI and relapse outcomes were reported over up to 24 and 36 weeks, respectively. The mean number of new T1 Gd+ lesions was numerically lower with natalizumab than with fingolimod by 4 weeks; accumulation rates were 0.02 and 0.09 per week, respectively, over 24 weeks (p=0.004). The cumulative probability of developing ≥1 lesion at 24 weeks was 40.7% with natalizumab versus 58.0% with fingolimod (HR=1.66; 95% CI 0.87 to 3.26; p=0.126); the corresponding probabilities for ≥2 lesions were 11.5% versus 48.5% (HR=4.05; 95% CI 1.47 to 11.14; p=0.007). No significant between-group differences were observed for the other MRI outcomes at 24 weeks. The cumulative probability of relapse over follow-up was 1.9% with natalizumab

versus 22.3% with fingolimod (HR=12.18; 95% CI 1.55 to 95.63; p=0.017). Adverse events were consistent with known safety profiles.

Conclusions These results suggest that natalizumab is more efficacious than fingolimod in reducing multiple sclerosis relapses and T1 Gd+ lesion accumulation in patients with active disease.

Clinicaltrials.gov registration number NCT02342704.

EudraCT registration number EUCTR2013-004622-29-IT.

Strengths and limitations of this study

- This study is the first randomised controlled trial to compare the efficacy of natalizumab and fingolimod in patients with relapsing-remitting multiple sclerosis.
- The primary endpoint, evolution of new on-treatment gadolinium-enhancing lesions to persistent black holes, could not be assessed due to early study termination.
- Secondary endpoints, including the effects of treatment on the development of new T1 gadolinium-enhancing lesions and new/newly enlarging T2 lesions, lesion volumes and relapse outcomes, were assessed over a relatively short treatment period of 24–36 weeks.

INTRODUCTION

Natalizumab and fingolimod are well-established, efficacious disease-modifying therapies for relapsing-remitting multiple sclerosis (RRMS), demonstrating reductions in clinical and radiological measures of disease activity in pivotal placebo-controlled trials.[1-5] Previous analyses have indicated that both natalizumab and fingolimod exhibit beneficial effects quickly (within 2 months) after treatment initiation,[6-9] which may be an important consideration in treatment selection, especially in patients with active disease. However, evidence regarding the relative efficacy of natalizumab and fingolimod has, to date, been limited to retrospective analyses of registry datasets.[10-22] While the majority of these studies reported improved outcomes with natalizumab compared with fingolimod,[10 12-15 18-21] several found no difference in clinical outcomes between the two therapies.[16 17] However, one study found that the reduction in annualised relapse rate (ARR) after 1 year of treatment was significantly greater with natalizumab than with fingolimod, whereas treatment persistence was significantly higher in patients treated with fingolimod.[22]

This study reports results from REVEAL, a 1-year, randomised, rater- and sponsor-blinded, prospective head-to-head study comparing natalizumab and fingolimod in patients with active RRMS. Although early study closure precluded analysis of the primary efficacy endpoint, available MRI data were used in unplanned exploratory analyses of secondary endpoints to directly compare natalizumab versus fingolimod efficacy within 4 weeks of therapy initiation. In addition, relapse data were analysed to assess ARRs and the cumulative probability of relapse over the duration of the study.

METHODS

REVEAL was a phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study conducted at 43 sites in nine countries between October 2014 and May 2016 (planned overall duration, 68 weeks) in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines (clinicaltrials.gov identifier NCT02342704; EudraCT identifier EUCTR2013-004622-29-IT).[23] The REVEAL investigators are listed in online supplementary table 1. All sites received institutional review board approval (online supplementary table 2), and all participants provided written informed consent. REVEAL was designed to include approximately 540 patients. However, after 1 year of enrolling patients, only 111 patients had been enrolled. The decision to terminate the study due to slow enrolment was made by the sponsor (Biogen) in November 2015. Outcome data were not made available until May 2016, and all scheduled MRI scans were evaluated in a blinded manner. Thus, the study termination decision was made without knowledge of the results.

Patients were aged 18–60 years and had active RRMS not previously treated with natalizumab, fingolimod or immunosuppressants, with ≥1 new T1 gadolinium-enhancing (Gd+) lesion within the 6 months prior to screening or ≥2 new T2 lesions on brain MRI within the 6 months prior to screening (compared with a T2-weighted scan 18 months before screening) as well as an Expanded Disability Status Scale (EDSS) score ≤5.5. Included patients could have previously been treated for ≥6 months with glatiramer acetate or an interferon beta formulation if they had ≥9 T2-hyperintense lesions on brain MRI and experienced ≥1 relapse while on therapy within the 6 months prior to screening. Multiple sclerosis (MS) treatment–naïve patients and patients who had

previously been treated for <6 months with glatiramer acetate or an interferon beta formulation were included only if they had ≥2 disabling relapses within the 12 months prior to screening. Patients with progressive MS were excluded.

Following a 4-week screening period, patients were randomly assigned (1:1) to open-label intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once daily for up to 52 weeks, then followed for up to 64 weeks. MRI scans were scheduled every 4 weeks for the first 24 weeks and then at 36 and 52 weeks. A follow-up visit approximately 12 weeks after the last dose of study drug was planned.

Relapses and adverse events (AEs) were assessed at scheduled visits. A clinical relapse was defined as new or recurrent neurological symptoms, not associated with fever, lasting for at least 24 hours and followed by a period of 30 days of stability or improvement. New or recurrent neurological symptoms that occurred fewer than 30 days after the onset of a protocol-defined relapse were considered part of the same relapse. MS relapses were not considered AEs, and MS relapses resulting in hospitalisation did not need to be reported as serious AEs (SAEs). However, any MS relapse that was complicated by other SAEs was reported as an SAE.

The intent-to-treat (ITT) population for efficacy analysis comprised all randomised subjects given ≥1 dose of study drug who provided any efficacy assessments. The primary endpoint (the evolution of new on-treatment T1-weighted Gd+ lesions to persistent black holes over 52 weeks) could not be assessed due to the lack of 52-week data. Secondary endpoints included the number of new T1 Gd+ lesions, the cumulative probability of developing new T1 Gd+ lesions, the number of new/newly enlarging T2 lesions, T1 and T2 lesion volumes and relapse outcomes. MRI and relapse outcomes

were assessed over the study duration according to the protocol. However, due to the limited numbers of events and patients at risk, MRI outcomes were reported over up to 24 weeks, while relapse outcomes were reported over up to 36 weeks. Other secondary endpoints, including no evidence of disease activity and change in information processing speed as measured by the Symbol Digit Modalities Test, were not interpretable due to the early closure of the study. Safety was assessed based on AEs, laboratory measurements, vital signs and physical examinations.

Treatment groups were compared using negative binomial regression models, and Cox regression models were developed for probability analyses. P values for comparisons in new T2 lesions and lesion volume changes were determined using a Wilcoxon rank-sum test.

A diffusion tensor imaging substudy including healthy volunteers was conducted to assess brain tissue damage and recovery in patients with active RRMS. Due to study termination, results were unevaluable.

Patient involvement

Patients were not involved in the design, conduct, reporting, or dissemination of this research.

RESULTS

The ITT population (table 1) comprised 108 patients (online supplementary figure 1); 63 patients (58.3%; natalizumab, n=32; fingolimod, n=31) received study treatment through

24 weeks, whereas only 3 (2.8%; natalizumab, n=2; fingolimod, n=1) were treated through 52 weeks (table 2). Median (range) follow-up time was 40.1 (7.1–64.7) weeks for natalizumab and 36.7 (7.0–64.1) weeks for fingolimod.

Table 1 Baseline demographics and characteristics

Characteristic	Natalizumab (n=54)	Fingolimod (n=54)
Age, years		
Mean (SD)	38.2 (8.8)	34.9 (8.7)
Median (min, max)	40 (21, 55)	35 (19, 55)
Sex, n (%) female	37 (68.5)	38 (70.4)
EDSS score		
Mean (SD)	2.5 (1.3)	2.6 (1.3)
Median (min, max)	2.0 (0.0, 6.0)	2.5 (0.0, 5.5)
Time since first MS symptoms, mean (SD), years	8.1 (7.7)	6.8 (7.0)
Time since MS diagnosis, mean (SD), years	5.0 (5.8)	4.5 (5.8)
Prior MS treatment, n (%) of patients*	26 (48.1)	28 (51.9)
Time since most recent relapse, mean (SD), days	86.8 (58.8)	91.2 (91.4)
Number of relapses in the past year, mean (SD)	1.9 (0.6)	1.9 (0.6)
Number of Gd+ lesions		
Mean (SD)	2.4 (3.6)	2.5 (4.9)
Median (min, max)	1 (0, 14)	1 (0, 28)
T2 lesion volume, mL		
Mean (SD)	11.9 (9.4)	10.9 (10.4)
Median (min, max)	8.5 (0.7, 40.1)	7.7 (0.1, 43.2)
T1-nonenhancing lesion volume, mL		
Mean (SD)	2.3 (2.4)	2.4 (3.4)
Median (min, max)	1.3 (0, 8.6)	1.1 (0, 15.3)

*Most commonly glatiramer acetate (natalizumab, n=7; fingolimod, n=9) and interferon beta (subcutaneous [SC] interferon beta-1a: natalizumab, n=10; fingolimod, n=6; intramuscular interferon beta-1a: natalizumab, n=4; fingolimod, n=10; SC interferon beta-1b: natalizumab, n=1, fingolimod, n=5; SC interferon beta-1b: natalizumab, n=1, fingolimod, n=2).
EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhanced; max, maximum; min, minimum; MS, multiple sclerosis; SD, standard deviation.

Table 2 Treatment exposure and safety outcomes

	Natalizumab (n=54)	Fingolimod (n=54)
Study drug exposure, days		
Mean (SD)	183.0 (90.9)	182.6 (101.8)
Median (range)	197 (1–364)	172 (1–362)
Patients receiving treatment at each time point, n (%)		
Baseline	54 (100)	54 (100)
Week 4	52 (96.3)	50 (92.6)
Week 8	50 (92.6)	47 (87.0)
Week 12	45 (83.3)	45 (83.3)
Week 16	42 (77.8)	40 (74.1)
Week 20	36 (66.7)	35 (64.8)
Week 24	32 (59.3)	31 (57.4)
Week 32	25 (46.3)	23 (42.6)
Week 40	11 (20.4)	13 (24.1)
Week 52	2 (3.7)	1 (1.9)
Treatment-emergent adverse events, n (%) of patients	23 (42.6)	32 (59.3)
Most commonly reported events, n (%) of patients*		
Headache	6 (11.1)	4 (7.4)
MS relapse	1 (1.9)	8 (14.8)
Hypoesthesia	0	3 (5.6)
Migraine	0	3 (5.6)
Upper respiratory tract infection	1 (1.9)	5 (9.3)
Urinary tract infection	2 (3.7)	3 (5.6)
Lymphocyte count decreased	0	5 (9.3)
Alanine aminotransferase increased	0	3 (5.6)
Anxiety	1 (1.9)	3 (5.6)
Fatigue	3 (5.6)	0
Oropharyngeal pain	3 (5.6)	1 (1.9)
Serious adverse events, n (%) of patients	0	2 (3.7)
Second-degree atrioventricular block	0	1 (1.9)
Migraine with aura	0	1 (1.9)
Events leading to study discontinuation, n (%) of patients†	1 (1.9)	3 (5.6)
Second-degree atrioventricular block	0	1 (1.9)
Infusion site rash	1 (1.9)	0
Alanine aminotransferase increased	0	1 (1.9)
Aspartate aminotransferase increased	0	1 (1.9)
Headache	0	1 (1.9)
Patients who discontinued, n (%)	53 (98.1)‡	51 (94.4)§

*Treatment-emergent adverse events reported by ≥5% patients in either group, listed by MedDRA preferred term.
†With the exception of atrioventricular block, adverse events leading to study discontinuation were classified as non-serious events.
‡Forty-nine patients discontinued due to sponsor study termination, two were lost to follow-up, one discontinued due to an AE and one discontinued due to withdrawal of consent.
§Forty-three patients discontinued due to sponsor study termination, three discontinued due to AEs, three discontinued due to physician decision, one was lost to follow-up and one discontinued for another reason.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; SD, standard deviation.

The mean number of new T1 Gd+ lesions was 63% lower in the natalizumab group than the fingolimod group at 4 weeks (p=0.353) and ≥70% lower at 12 weeks (p=0.030; figure 1), a difference that was maintained (with reduced patient numbers) through 24 weeks (p=0.008). Over 24 weeks, new T1 Gd+ lesion accumulation was lower among natalizumab- than fingolimod-treated patients (0.02 vs 0.09 new lesions per week; p=0.004). Over the entire follow-up period, natalizumab-treated patients were significantly less likely than fingolimod-treated patients to develop ≥2 or ≥3 new T1 Gd+ lesions (table 3). No significant between-group differences were observed in other MRI outcomes at 24 weeks; however, all MRI results numerically favoured natalizumab (table 3).

Table 3 Key MRI and clinical outcomes

Outcomes	Natalizumab (n=54)	Fingolimod (n=54)	HR (95% CI)	p value*
MRI outcomes: T1 Gd+ lesions				
Cumulative probability of developing new T1 Gd+ lesions over study, %				
≥1	40.68	57.99	1.68 (0.86 to 3.25)	0.126
≥2	11.54	48.48	4.05 (1.47 to 11.14)	0.007
≥3	10.02	41.38	4.09 (1.29 to 12.89)	0.016
Number of patients with new T1 Gd+ lesions from baseline to 24 weeks, n/N (%)	16/47 (34.0)†	24/45 (53.3)†	NA	0.062
Change from baseline in T1 Gd+ lesion volume to 24 weeks, mean (SD)	0.5 (31.2)‡	1.8 (19.7)‡	NA	0.532
MRI outcomes: T2 lesions				
Number of patients with new/newly enlarging T2 lesions at 24 weeks, n/N (%)	6/15 (40.0)	10/16 (62.5)	NA	0.210
Number of new/newly enlarging T2 lesions at 24 weeks per patient, mean (SD)	1.3 (2.5)‡	1.9 (2.2)‡	NA	0.263
Change from baseline in T2 lesion volume to 24 weeks, mean (SD)	0.1 (4.4)‡	3.3 (5.0)‡	NA	0.053
Relapse outcomes				
Cumulative probability of relapse over study, %§	1.9	22.3	12.18 (1.55 to 95.63)¶	0.017
ARR on study (95% CI)	0.02 (0.00 to 0.13)	0.20 (0.11 to 0.37)	10.91 (1.39 to 85.70)**	0.023††

*p value based on a Cox model adjusted for the baseline number of Gd+ lesions, age, baseline EDSS score and years since first symptom (for the cumulative probability of new T1 Gd+ lesions during follow-up), from a chi-square test between the two treatment groups (for the number of patients with new lesions) or based on a Wilcoxon rank-sum test between the two treatment groups (for the number of new/newly enlarging T2 lesions and changes in lesion volume).
†Includes patients with new T1 Gd+ lesions at any time point after baseline. Not all patients received treatment through 24 weeks.
‡Natalizumab, n=15; fingolimod, n=16. Includes only patients who had MRI data through 24 weeks.
§Cumulative probabilities at 36 weeks are reported, as no relapse events were observed after 36 weeks.
¶Based on Cox model adjusted for the number of relapses in the year before baseline, age, baseline EDSS score and years since first symptom.
**Value indicated is a rate ratio based on a negative binomial model of ARR with treatment as effect, adjusted for the number of relapses in the year before baseline, years since first symptom, baseline EDSS score and baseline age.
††p value based on a negative binomial model of ARR with treatment as effect, adjusted for the number of relapses in the year before baseline, years since first symptom, baseline EDSS score and baseline age.
ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MS, multiple sclerosis; NA, not applicable.

During follow-up in this abbreviated study, natalizumab-treated patients were significantly less likely than fingolimod-treated patients to experience a relapse (table 3). The cumulative probability of relapse over follow-up was 1.9% with natalizumab and 22.3% with fingolimod (HR=12.18; 95% CI 1.55 to 95.63; p=0.017; figure 2A). Pre-treatment annualised relapse rates in the natalizumab and fingolimod treatment groups were 1.91 and 1.87, respectively (figure 2B). The on-treatment ARR was 0.02 in the natalizumab group (a 99% reduction) and 0.20 in the fingolimod group (an 89% reduction). The on-treatment ARR was 90% lower with natalizumab than with fingolimod (p=0.023).

Treatment-emergent AEs were reported for 42.6% and 59.3% of natalizumab- and fingolimod-treated patients, respectively, including two serious AEs, both in patients on fingolimod (table 2). All safety findings were consistent with the known safety profiles for natalizumab and fingolimod.[24 25]

DISCUSSION

These unplanned exploratory analyses of REVEAL secondary endpoints indicate that natalizumab reduces T1 Gd+ lesion accumulation and relapse disease activity soon after initiation, consistent with previous clinical trial findings.[6 7] Treatment effects on MRI outcomes were observed within 4 weeks of starting natalizumab.

While both treatments were efficacious in patients with active RRMS, reduction in disease activity, measured by the number of new T1 Gd+ lesions and relapses, occurred more rapidly and to a greater extent with natalizumab than with fingolimod.

These results extend previous findings of the efficacy advantage of natalizumab over fingolimod in preventing relapses and reducing disease activity from comparative analyses of patients with active RRMS or prior treatment failure followed up for 1–2 years in real-world settings.[10-13 15 19] No significant between-group differences were observed for other MRI outcomes, such as lesion volume and the number of new/newly enlarging T2 lesions.

Safety findings in this study were consistent with the established profile of each treatment, with no new safety concerns noted.[24 25]

Although REVEAL was designed as a randomised controlled trial, results should be interpreted with caution, as analysis of the primary endpoint was not possible due to early study closure. However, bias in the results due to early study termination is unlikely based on the timing of the decision (before outcome data availability) and the blinding of the sponsor and MRI readers. Secondary efficacy evaluations were limited to a relatively short treatment period of 24–36 weeks, precluding meaningful assessment of EDSS score change. A further limitation is that the long-term consequences of these relatively short-term findings are unknown.

In conclusion, the results suggest greater benefit with natalizumab than with fingolimod in reducing relapse rates and T1 Gd+ lesion accumulation in patients with active RRMS. The onset of efficacy occurred more rapidly with natalizumab than with fingolimod, which may be an important consideration for treatment selection in patients with active disease, who need swift and effective control of disease activity.

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Competing interests HB has received compensation for consulting from Biogen, Merck Serono and Novartis and research support from Biogen and Merck Serono. SL and NC are employees of and may hold stock and/or stock options in Biogen. DJ has received research funding from Biogen and Genentech and personal compensation for speaking or consulting services from Acorda, Bayer, Biogen, Genentech,

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Patient consent Obtained.

Ethics approval The study was approved by ethics committees for all participating study centres.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability Datasets from this study are not publicly available. Requests for de-identified data should be made to Biogen via established company data-sharing policies as detailed on the website http://clinicalresearch.biogen.com/.

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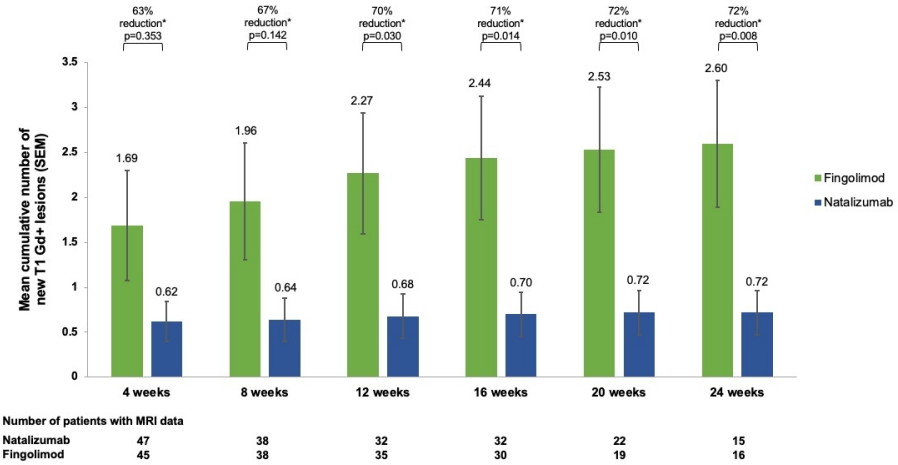
FIGURE LEGENDS

Figure 1 Mean cumulative number of new Gd+ lesions on T1-weighted MRI scans reported over 24 weeks. *Reduction is for natalizumab versus fingolimod. P value is based on a negative binomial regression model adjusted for baseline T1 Gd+ lesion count. Gd+, gadolinium enhancing; SEM, standard error of the mean.

Figure 2 Impact of natalizumab versus fingolimod treatment on relapse outcomes, shown as (A) Kaplan-Meier survival curve of time to relapse over 52 weeks and (B) ARRs before study and on study. *Fingolimod versus natalizumab, based on a Cox model adjusted for number of relapses in the year before baseline, age, baseline EDSS score and years since first symptom. †The x-axis has been truncated at week 36, as no events were observed after week 36. ‡p value is based on a negative binomial model of ARR with treatment as effect, adjusted for number of relapses in the year before baseline, years since first symptom, baseline EDSS score and baseline age. ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale.



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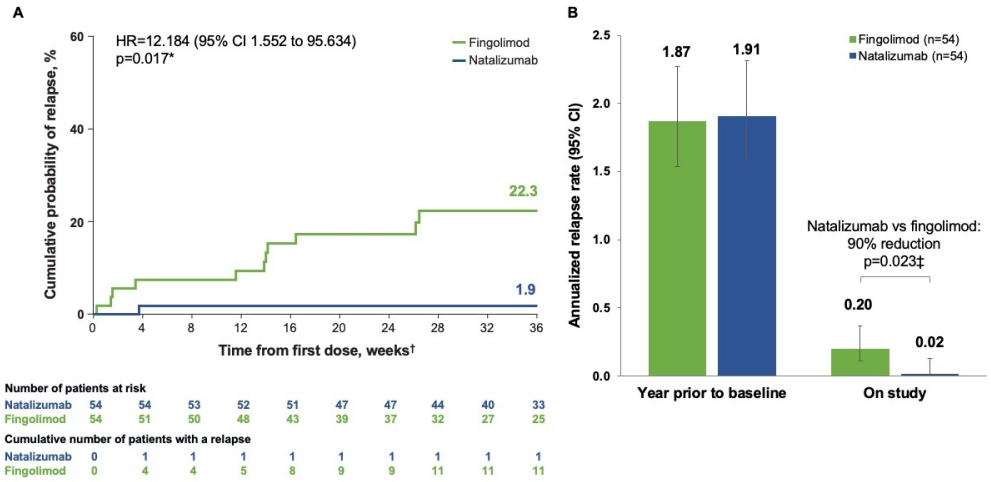

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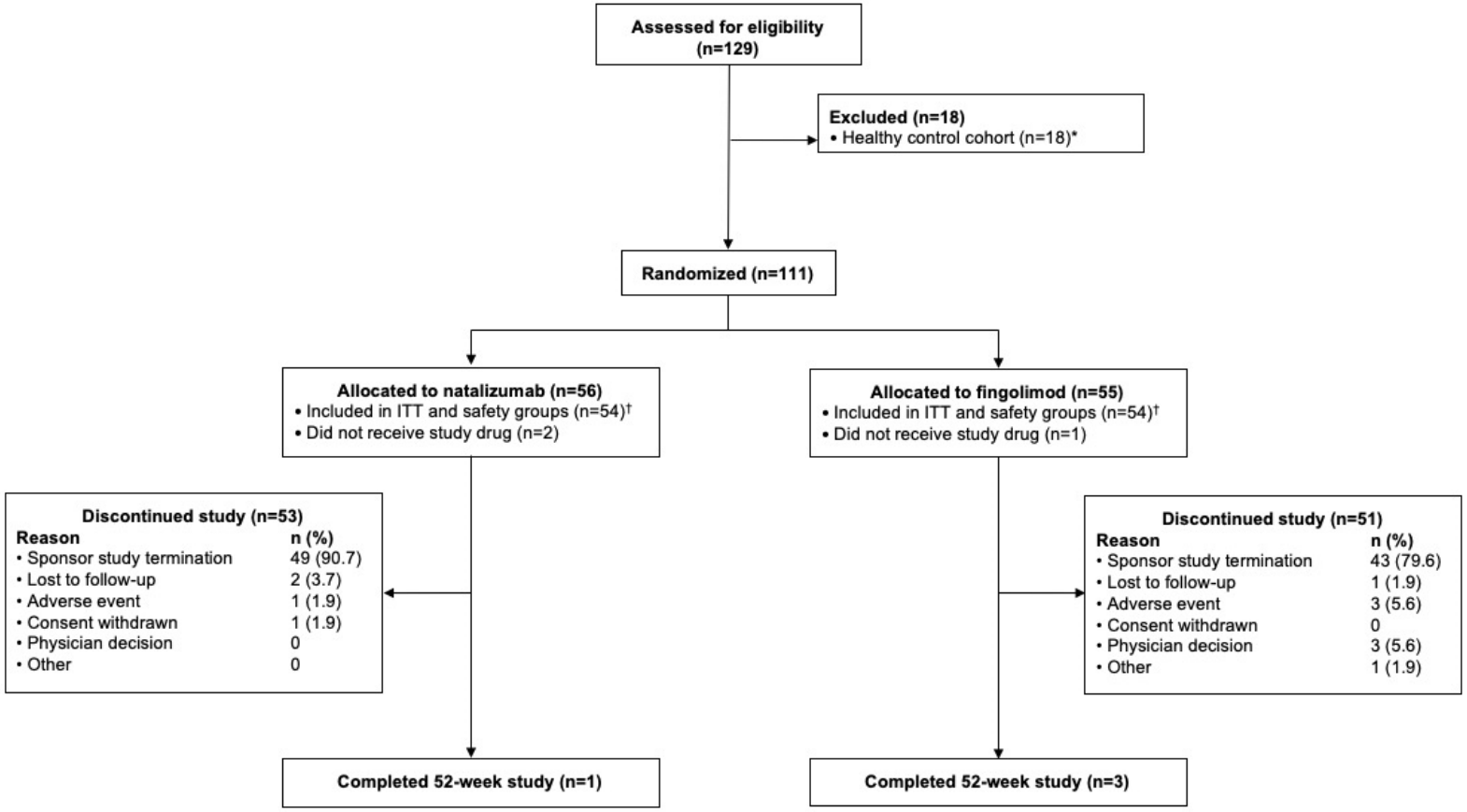
Peiqing Qian	Swedish Medical Center, Seattle, WA, USA	Site investigator	Participated in data collection
Enrique Alvarez	University of Colorado, Aurora, CO, USA	Site investigator	Participated in data collection
Bruce Hughes	Ruan Neurology Clinical Research Center, Des Moines, IA, USA	Site investigator	Participated in data collection
Douglas R. Jeffery	Research Institute of the Carolinas, PLC, Huntersville, NC, USA	Site investigator	Participated in data collection
John Huddlestone	MultiCare Health System Institute for Research and Innovation, Tacoma, WA, USA	Site investigator	Participated in data collection
Sibyl Wray	Hope Neurology, Knoxville, TN, USA	Site investigator	Participated in data collection

Online supplementary table 2 Ethics committees

Austin Health Human Research Ethics Committee (RGO)
Azienda Ospedaliera Universitaria Policlinico Umberto I–Università di Roma La Sapienza
Azienda Ospedaliero Universitaria San Martino
Azienda Socio Sanitaria Territoriale Sette Laghi (Presidio Ospedale di Circolo e Fondazione Macchi)
CEIC Autonomico de Andalucia
CEIC Complejo Hospitalario de León
CEIC de Aragón (CEICA)
CEIC de Galicia
CEIC Hospital Universitario Nuestra Señora de la Candelaria
CEIC Hospital Virgen de la Arrixaca
CEIC Islas Baleares
Comitato Etico della Azienda Ospedaliero Universitaria di Cagliari
Comitato Etico dell'Azienda Ospedaliera Universitaria S. Luigi Gonzaga di Orbassano
Comitato Etico dell'IRCCS Centro Neurolesi Bonino Pulejo di Messina
Comitato Etico IRCCS Ospedale S. Raffaele di Milano
Comitato Etico Lazio 1
Comitato Etico Palermo 1
Comitato Etico per le attività biomediche "Carlo Romano"
Copernicus Group IRB
Eastern Health Research and Ethics Committee (RGO)
Eticka komise Fakultni nemocnice Hradec Kralove
Eticka komise Fakultni nemocnice Ostrava
Eticka komise Fakultni nemocnice u sv. Anny v Brne
Eticka komise FN a LF UP Olomouc
Eticka komise Krajska zdravotni a.s.–Nemocnice Teplice o.z.
Eticka komise Pardubicke krajske nemocnice
Eticka komise pri Nemocnici Jihlava
Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice v Motole
Hospital del Mar
Hospital Universitari de Girona Dr Josep Trueta
Hospital Universitari i Politecnic La Fe
Hospital Universitari Vall d'Hebron
Hospital Universitario de La Princesa
Hunter New England Local Health District (RGO)
Melbourne Health Human Research Ethics Committee (RGO)
Mercy Medical Center–DSM
Multicentricka eticka komise Fakultni nemocnice Brno
Rhode Island Hospital IRB
Rush University Medical Center

Seconda Università degli Studi di Napoli
Servizo Galego de Saúde
University of New Mexico HRPO
University of Pennsylvania IRB
University of Sydney (RGO)
University of Texas Southwestern Investigational Review Board
University of Texas Health Science Center at San Antonio Institutional Review Board
Wheaton Franciscan Healthcare IRB
Western Institutional Review Board

Online supplementary figure 1 Patient flow



*Healthy control subjects were screened as part of the diffusion tensor imaging substudy being conducted along with the main study in patients with relapsing-remitting multiple sclerosis. These patients were not treated with natalizumab or fingolimod and were not included in the main study results.
†The safety group comprised all randomised patients who received at least one dose of study drug; the ITT group comprised all randomised patients who received at least one dose of study drug and provided at least one efficacy assessment.
ITT, intent-to-treat.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3–4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5–6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5–6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6–7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7–8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7–8
Sample size	7a	How sample size was determined	6, 8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5–6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13–14
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study

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Natalizumab versus fingolimod for patients with active relapsing-remitting multiple sclerosis: results from REVEAL, a prospective, randomised head-to-head study

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ABSTRACT

Objective To directly compare the efficacy of natalizumab and fingolimod in patients with active relapsing-remitting multiple sclerosis.

Methods This phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study was conducted at 43 sites in nine countries. Patients were randomised (1:1) to intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once daily for ≤52 weeks. Enrolment-related early study termination precluded assessment of the primary endpoint (evolution of new on-treatment gadolinium-enhancing [Gd+] lesions to persistent black holes). Unplanned exploratory analyses of secondary endpoints evaluated the effects of treatment on the development of new T1 Gd+ lesions and new/newly enlarging T2 lesions, lesion volumes and relapse outcomes.

Results The intent-to-treat population comprised 108 patients (natalizumab, n=54; fingolimod, n=54); 63 completed ≥24 weeks of treatment. Due to the limited numbers of events and patients at risk, MRI and relapse outcomes were reported over up to 24 and 36 weeks, respectively. The mean number of new T1 Gd+ lesions was numerically lower with natalizumab than with fingolimod by 4 weeks; accumulation rates were 0.02 and 0.09 per week, respectively, over 24 weeks (p=0.004). The cumulative probability of developing ≥1 lesion at 24 weeks was 40.7% with natalizumab versus 58.0% with fingolimod (HR=1.66; 95% CI 0.87 to 3.26; p=0.126); the corresponding probabilities for ≥2 lesions were 11.5% versus 48.5% (HR=4.05; 95% CI 1.47 to 11.14; p=0.007). No significant between-group differences were observed for the other MRI outcomes at 24 weeks. The cumulative probability of relapse over follow-up was 1.9% with natalizumab

versus 22.3% with fingolimod (HR=12.18; 95% CI 1.55 to 95.63; p=0.017). Adverse events were consistent with known safety profiles.

Conclusions These results suggest that natalizumab is more efficacious than fingolimod in reducing multiple sclerosis relapses and T1 Gd+ lesion accumulation in patients with active disease.

Clinicaltrials.gov registration number NCT02342704.

EudraCT registration number EUCTR2013-004622-29-IT.

Strengths and limitations of this study

- This study is the first randomised controlled trial to compare the efficacy of natalizumab and fingolimod in patients with relapsing-remitting multiple sclerosis.
- The primary endpoint, evolution of new on-treatment gadolinium-enhancing lesions to persistent black holes, could not be assessed due to early study termination.
- Secondary endpoints, including the effects of treatment on the development of new T1 gadolinium-enhancing lesions and new/newly enlarging T2 lesions, lesion volumes and relapse outcomes, were assessed over a relatively short treatment period of 24–36 weeks.

INTRODUCTION

Natalizumab and fingolimod are well-established, efficacious disease-modifying therapies for relapsing-remitting multiple sclerosis (RRMS), demonstrating reductions in clinical and radiological measures of disease activity in pivotal placebo-controlled trials.[1-5] Previous analyses have indicated that both natalizumab and fingolimod exhibit beneficial effects quickly (within 2 months) after treatment initiation,[6-9] which may be an important consideration in treatment selection, especially in patients with active disease. However, evidence regarding the relative efficacy of natalizumab and fingolimod has, to date, been limited to retrospective analyses of registry datasets.[10-22] While the majority of these studies reported improved outcomes with natalizumab compared with fingolimod,[10 12-15 18-21] several found no difference in clinical outcomes between the two therapies.[16 17] However, one study found that the reduction in annualised relapse rate (ARR) after 1 year of treatment was significantly greater with natalizumab than with fingolimod, whereas treatment persistence was significantly higher in patients treated with fingolimod.[22]

This study reports results from REVEAL, a 1-year, randomised, rater- and sponsor-blinded, prospective head-to-head study comparing natalizumab and fingolimod in patients with active RRMS. Although early study closure precluded analysis of the primary efficacy endpoint, available MRI data were used in unplanned exploratory analyses of secondary endpoints to directly compare natalizumab versus fingolimod efficacy within 4 weeks of therapy initiation. In addition, relapse data were analysed to assess ARRs and the cumulative probability of relapse over the duration of the study.

METHODS

REVEAL was a phase 4, randomised, rater- and sponsor-blinded, prospective, parallel-group, clinic-based head-to-head study conducted at 43 sites in nine countries between October 2014 and May 2016 (planned overall duration, 68 weeks) in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines (clinicaltrials.gov identifier NCT02342704; EudraCT identifier EUCTR2013-004622-29-IT).[23] The REVEAL investigators are listed in online supplementary table 1. All sites received institutional review board approval (online supplementary table 2), and all participants provided written informed consent. REVEAL was designed to include approximately 540 patients. However, after 1 year of enrolling patients, only 111 patients had been enrolled. The decision to terminate the study due to slow enrolment was made by the sponsor (Biogen) in November 2015. Outcome data were not made available until May 2016, and all scheduled MRI scans were evaluated in a blinded manner. Thus, the study termination decision was made without knowledge of the results.

Patients were aged 18–60 years and had active RRMS not previously treated with natalizumab, fingolimod or immunosuppressants, with ≥1 new T1 gadolinium-enhancing (Gd+) lesion within the 6 months prior to screening or ≥2 new T2 lesions on brain MRI within the 6 months prior to screening (compared with a T2-weighted scan 18 months before screening) as well as an Expanded Disability Status Scale (EDSS) score ≤5.5. Included patients could have previously been treated for ≥6 months with glatiramer acetate or an interferon beta formulation if they had ≥9 T2-hyperintense lesions on brain MRI and experienced ≥1 relapse while on therapy within the 6 months prior to screening. Multiple sclerosis (MS) treatment–naïve patients and patients who had

previously been treated for <6 months with glatiramer acetate or an interferon beta formulation were included only if they had ≥2 disabling relapses within the 12 months prior to screening. Patients with progressive MS were excluded.

Following a 4-week screening period, patients were randomly assigned (1:1) to open-label intravenous natalizumab 300 mg every 4 weeks or oral fingolimod 0.5 mg once daily for up to 52 weeks, then followed for up to 64 weeks. MRI scans were scheduled every 4 weeks for the first 24 weeks and then at 36 and 52 weeks. A follow-up visit approximately 12 weeks after the last dose of study drug was planned.

Relapses and adverse events (AEs) were assessed at scheduled visits. A clinical relapse was defined as new or recurrent neurological symptoms, not associated with fever, lasting for at least 24 hours and followed by a period of 30 days of stability or improvement. New or recurrent neurological symptoms that occurred fewer than 30 days after the onset of a protocol-defined relapse were considered part of the same relapse. MS relapses were not considered AEs, and MS relapses resulting in hospitalisation did not need to be reported as serious AEs (SAEs). However, any MS relapse that was complicated by other SAEs was reported as an SAE.

The intent-to-treat (ITT) population for efficacy analysis comprised all randomised subjects given ≥1 dose of study drug who provided any efficacy assessments. The primary endpoint (the evolution of new on-treatment T1-weighted Gd+ lesions to persistent black holes over 52 weeks) could not be assessed due to the lack of 52-week data. Secondary endpoints included the number of new T1 Gd+ lesions, the cumulative probability of developing new T1 Gd+ lesions, the number of new/newly enlarging T2 lesions, T1 and T2 lesion volumes and relapse outcomes. MRI and relapse outcomes

were assessed over the study duration according to the protocol. However, due to the limited numbers of events and patients at risk, MRI outcomes were reported over up to 24 weeks, while relapse outcomes were reported over up to 36 weeks. Other secondary endpoints, including time to complete recovery from first relapse, proportion of patients with no evidence of disease activity and change from baseline in information processing speed as measured by the Symbol Digit Modalities Test, were not interpretable due to the early closure of the study. Safety was assessed based on AEs, laboratory measurements, vital signs and physical examinations.

Treatment groups were compared using negative binomial regression models, and Cox regression models were developed for probability analyses. P values for comparisons in new T2 lesions and lesion volume changes were determined using a Wilcoxon rank-sum test.

A diffusion tensor imaging substudy including healthy volunteers was conducted to assess brain tissue damage and recovery in patients with active RRMS. Due to study termination, results were unevaluable.

Patient involvement

Patients were not involved in the design, conduct, reporting, or dissemination of this research.

RESULTS

The ITT population (table 1) comprised 108 patients (online supplementary figure 1); 63 patients (58.3%; natalizumab, n=32; fingolimod, n=31) received study treatment through 24 weeks, whereas only 3 (2.8%; natalizumab, n=2; fingolimod, n=1) were treated through 52 weeks (table 2). Median (range) follow-up time was 40.1 (7.1–64.7) weeks for natalizumab and 36.7 (7.0–64.1) weeks for fingolimod.

Table 1 Baseline demographics and characteristics

Characteristic	Natalizumab (n=54)	Fingolimod (n=54)
Age, years		
Mean (SD)	38.2 (8.8)	34.9 (8.7)
Median (min, max)	40 (21, 55)	35 (19, 55)
Sex, n (%) female	37 (68.5)	38 (70.4)
EDSS score		
Mean (SD)	2.5 (1.3)	2.6 (1.3)
Median (min, max)	2.0 (0.0, 6.0)	2.5 (0.0, 5.5)
Time since first MS symptoms, mean (SD), years	8.1 (7.7)	6.8 (7.0)
Time since MS diagnosis, mean (SD), years	5.0 (5.8)	4.5 (5.8)
Prior MS treatment, n (%) of patients*	26 (48.1)	28 (51.9)
Time since most recent relapse, mean (SD), days	86.8 (58.8)	91.2 (91.4)
Number of relapses in the past year, mean (SD)	1.9 (0.6)	1.9 (0.6)
Number of Gd+ lesions		
Mean (SD)	2.4 (3.6)	2.5 (4.9)
Median (min, max)	1 (0, 14)	1 (0, 28)
T2 lesion volume, mL		
Mean (SD)	11.9 (9.4)	10.9 (10.4)
Median (min, max)	8.5 (0.7, 40.1)	7.7 (0.1, 43.2)
T1-nonenhancing lesion volume, mL		
Mean (SD)	2.3 (2.4)	2.4 (3.4)
Median (min, max)	1.3 (0, 8.6)	1.1 (0, 15.3)

*Most commonly glatiramer acetate (natalizumab, n=7; fingolimod, n=9) and interferon beta (subcutaneous [SC] interferon beta-1a: natalizumab, n=10; fingolimod, n=6; intramuscular interferon beta-1a: natalizumab, n=4; fingolimod, n=10; SC interferon beta-1b: natalizumab, n=1, fingolimod, n=5; SC interferon beta-1b: natalizumab, n=1, fingolimod, n=2).
EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhanced; max, maximum; min, minimum; MS, multiple sclerosis; SD, standard deviation.

Table 2 Treatment exposure and safety outcomes

	Natalizumab (n=54)	Fingolimod (n=54)
Study drug exposure, days		
Mean (SD)	183.0 (90.9)	182.6 (101.8)
Median (range)	197 (1–364)	172 (1–362)
Patients receiving treatment at each time point, n (%)		
Baseline	54 (100)	54 (100)
Week 4	52 (96.3)	50 (92.6)
Week 8	50 (92.6)	47 (87.0)
Week 12	45 (83.3)	45 (83.3)
Week 16	42 (77.8)	40 (74.1)
Week 20	36 (66.7)	35 (64.8)
Week 24	32 (59.3)	31 (57.4)
Week 32	25 (46.3)	23 (42.6)
Week 40	11 (20.4)	13 (24.1)
Week 52	2 (3.7)	1 (1.9)
Treatment-emergent adverse events, n (%) of patients	23 (42.6)	32 (59.3)
Most commonly reported events, n (%) of patients*		
Headache	6 (11.1)	4 (7.4)
MS relapse	1 (1.9)	8 (14.8)
Hypoesthesia	0	3 (5.6)
Migraine	0	3 (5.6)
Upper respiratory tract infection	1 (1.9)	5 (9.3)
Urinary tract infection	2 (3.7)	3 (5.6)
Lymphocyte count decreased	0	5 (9.3)
Alanine aminotransferase increased	0	3 (5.6)
Anxiety	1 (1.9)	3 (5.6)
Fatigue	3 (5.6)	0
Oropharyngeal pain	3 (5.6)	1 (1.9)
Serious adverse events, n (%) of patients	0	2 (3.7)
Second-degree atrioventricular block	0	1 (1.9)
Migraine with aura	0	1 (1.9)
Events leading to study discontinuation, n (%) of patients†	1 (1.9)	3 (5.6)
Second-degree atrioventricular block	0	1 (1.9)
Infusion site rash	1 (1.9)	0
Alanine aminotransferase increased	0	1 (1.9)
Aspartate aminotransferase increased	0	1 (1.9)
Headache	0	1 (1.9)
Patients who discontinued, n (%)	53 (98.1)‡	51 (94.4)§

*Treatment-emergent adverse events reported by ≥5% patients in either group, listed by MedDRA preferred term.
†With the exception of atrioventricular block, adverse events leading to study discontinuation were classified as non-serious events.
‡Forty-nine patients discontinued due to sponsor study termination, two were lost to follow-up, one discontinued due to an AE and one discontinued due to withdrawal of consent.
§Forty-three patients discontinued due to sponsor study termination, three discontinued due to AEs, three discontinued due to physician decision, one was lost to follow-up and one discontinued for another reason.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MS, multiple sclerosis; SD, standard deviation.

The mean number of new T1 Gd+ lesions was 63% lower in the natalizumab group than the fingolimod group at 4 weeks (p=0.353) and ≥70% lower at 12 weeks (p=0.030; figure 1), a difference that was maintained (with reduced patient numbers) through 24 weeks (p=0.008). Over 24 weeks, new T1 Gd+ lesion accumulation was lower among natalizumab- than fingolimod-treated patients (0.02 vs 0.09 new lesions per week; p=0.004). Over the entire follow-up period, natalizumab-treated patients were significantly less likely than fingolimod-treated patients to develop ≥2 or ≥3 new T1 Gd+ lesions (table 3). No significant between-group differences were observed in other MRI outcomes at 24 weeks; however, all MRI results numerically favoured natalizumab (table 3).

Table 3 Key MRI and clinical outcomes

Outcomes	Natalizumab (n=54)	Fingolimod (n=54)	HR (95% CI)*	p value†
MRI outcomes: T1 Gd+ lesions				
Cumulative probability of developing new T1 Gd+ lesions over study, %				
≥1	40.68	57.99	0.60 (0.31 to 1.16)	0.126
≥2	11.54	48.48	0.25 (0.09 to 0.68)	0.007
≥3	10.02	41.38	0.24 (0.08 to 0.78)	0.016
Number of patients with new T1 Gd+ lesions from baseline to 24 weeks, n/N (%)	16/47 (34.0)‡	24/45 (53.3)‡	NA	0.062
Change from baseline in T1 Gd+ lesion volume to 24 weeks, mean (SD)	0.5 (31.2)§	1.8 (19.7)§	NA	0.532
MRI outcomes: T2 lesions				
Number of patients with new/newly enlarging T2 lesions at 24 weeks, n/N (%)	6/15 (40.0)	10/16 (62.5)	NA	0.210
Number of new/newly enlarging T2 lesions at 24 weeks per patient, mean (SD)	1.3 (2.5)§	1.9 (2.2)§	NA	0.263
Change from baseline in T2 lesion volume to 24 weeks, mean (SD)	0.1 (4.4)§	3.3 (5.0)§	NA	0.053
Relapse outcomes				
Cumulative probability of relapse over study, %¶	1.9	22.3	0.08 (0.01 to 0.64)**	0.017
ARR on study (95% CI)	0.02 (0.00 to 0.13)	0.20 (0.11 to 0.37)	0.09 (0.01 to 0.72)††	0.023‡‡

*All HRs and rate ratios compare natalizumab to fingolimod.
†p value based on a Cox model adjusted for the baseline number of Gd+ lesions, age, baseline EDSS score and years since first symptom (for the cumulative probability of new T1 Gd+ lesions during follow-up), from a chi-square test between the two treatment groups (for the number of patients with new lesions) or based on a Wilcoxon rank-sum test between the two treatment groups (for the number of new/newly enlarging T2 lesions and changes in lesion volume).
‡Includes patients with new T1 Gd+ lesions at any time point after baseline. Not all patients received treatment through 24 weeks.
§Natalizumab, n=15; fingolimod, n=16. Includes only patients who had MRI data through 24 weeks.
¶Cumulative probabilities at 36 weeks are reported, as no relapse events were observed after 36 weeks.
**Based on Cox model adjusted for the number of relapses in the year before baseline, age, baseline EDSS score and years since first symptom.
††Value indicated is a rate ratio based on a negative binomial model of ARR with treatment as effect, adjusted for the number of relapses in the year before baseline, years since first symptom, baseline EDSS score and baseline age.
‡‡p value based on a negative binomial model of ARR with treatment as effect, adjusted for the number of relapses in the year before baseline, years since first symptom, baseline EDSS score and baseline age.
ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancing; MS, multiple sclerosis; NA, not applicable.

During follow-up in this abbreviated study, natalizumab-treated patients were significantly less likely than fingolimod-treated patients to experience a relapse (table 3). The cumulative probability of relapse over follow-up was 1.9% with natalizumab and 22.3% with fingolimod (HR=0.08; 95% CI 0.01 to 0.64; p=0.017; figure 2A). Pre-treatment annualised relapse rates in the natalizumab and fingolimod treatment groups were 1.91 and 1.87, respectively (figure 2B). The on-treatment ARR was 0.02 in the natalizumab group (a 99% reduction) and 0.20 in the fingolimod group (an 89% reduction). The on-treatment ARR was 90% lower with natalizumab than with fingolimod (p=0.023).

Treatment-emergent AEs were reported for 42.6% and 59.3% of natalizumab- and fingolimod-treated patients, respectively, including two serious AEs, both in patients on fingolimod (table 2). All safety findings were consistent with the known safety profiles for natalizumab and fingolimod.[24 25]

DISCUSSION

These unplanned exploratory analyses of REVEAL secondary endpoints indicate that natalizumab reduces T1 Gd+ lesion accumulation and relapse disease activity soon after initiation, consistent with previous clinical trial findings.[6 7] Treatment effects on MRI outcomes were observed within 4 weeks of starting natalizumab.

While both treatments were efficacious in patients with active RRMS, reduction in disease activity, measured by the number of new T1 Gd+ lesions and relapses, occurred more rapidly and to a greater extent with natalizumab than with fingolimod.

These results extend previous findings of the efficacy advantage of natalizumab over fingolimod in preventing relapses and reducing disease activity from comparative analyses of patients with active RRMS or prior treatment failure followed up for 1–2 years in real-world settings.[10-13 15 19] No significant between-group differences were observed for other MRI outcomes, such as lesion volume and the number of new/newly enlarging T2 lesions.

Safety findings in this study were consistent with the established profile of each treatment, with no new safety concerns noted.[24 25]

Although REVEAL was designed as a randomised controlled trial, results should be interpreted with caution, as analysis of the primary endpoint was not possible due to early study closure. However, bias in the results due to early study termination is unlikely based on the timing of the decision (before outcome data availability) and the blinding of the sponsor and MRI readers. Secondary efficacy evaluations were limited to a relatively short treatment period of 24–36 weeks, precluding meaningful assessment of EDSS score change. A further limitation is that the long-term consequences of these relatively short-term findings are unknown.

In conclusion, the results suggest greater benefit with natalizumab than with fingolimod in reducing relapse rates and T1 Gd+ lesion accumulation in patients with active RRMS. The onset of efficacy occurred more rapidly with natalizumab than with fingolimod, which may be an important consideration for treatment selection in patients with active disease, who need swift and effective control of disease activity.

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Contributors HB, DJ, DLA, MF, JJGG and P-RH: study design. HB, SL, DJ, DLA, MF, JJGG, SS, NC and P-RH: analysis and interpretation of data. HB, SL and P-RH: manuscript development. HB, SL, DJ, DLA, MF, JJGG, SS, NC and P-RH: revising the manuscript for intellectual content.

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Competing interests HB has received compensation for consulting from Biogen, Merck Serono and Novartis and research support from Biogen and Merck Serono. SL and NC are employees of and may hold stock and/or stock options in Biogen. DJ has received research funding from Biogen and Genentech and personal compensation for speaking or consulting services from Acorda, Bayer, Biogen, Genentech,

GlaxoSmithKline, Novartis, Questcor, Serono and Teva. DLA has served on advisory boards for, received speaker honoraria from, served as a consultant for or received research support from Bayer, Biogen, Coronado Biosciences, the Consortium of Multiple Sclerosis Centers, Eli Lilly, EMD Serono, Genentech, Genzyme, GlaxoSmithKline, Merck Serono, MS Forum, NeuroRx Research, Novartis, Opexa Therapeutics, Roche, Teva, the Canadian Institutes of Health Research, the Multiple Sclerosis Society of Canada and the SA Serono Symposia International Foundation, and he holds stock in NeuroRx Research. MF is editor-in-chief of the *Journal of Neurology*; has received compensation for consulting services and/or speaking activities from Biogen, Merck Serono, Novartis and Teva; and has received research support from Biogen, Merck Serono, Novartis, Roche, Teva, the Italian Ministry of Health, la Fondazione Italiana Sclerosi Multipla (FISM) and la Fondazione Italiana di Ricerca per la Sclerosi Laterale Amiotrofica (AriSLA). JJGG serves on the editorial boards of *Multiple Sclerosis Journal* and *Neurology*; has received speaker honoraria from Biogen, Genzyme, Merck Serono, Novartis and Teva; has received research support from Biogen; and has served on the boards of the Dutch MS Research Foundation and the Progressive MS Alliance. SS and P-RH were employees of Biogen at the time of these analyses and may hold stock and/or stock options in Biogen.

Patient consent Obtained.

Ethics approval The study was approved by ethics committees for all participating study centres.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability Datasets from this study are not publicly available. Requests for de-identified data should be made to Biogen via established company data-sharing policies as detailed on the website http://clinicalresearch.biogen.com/.

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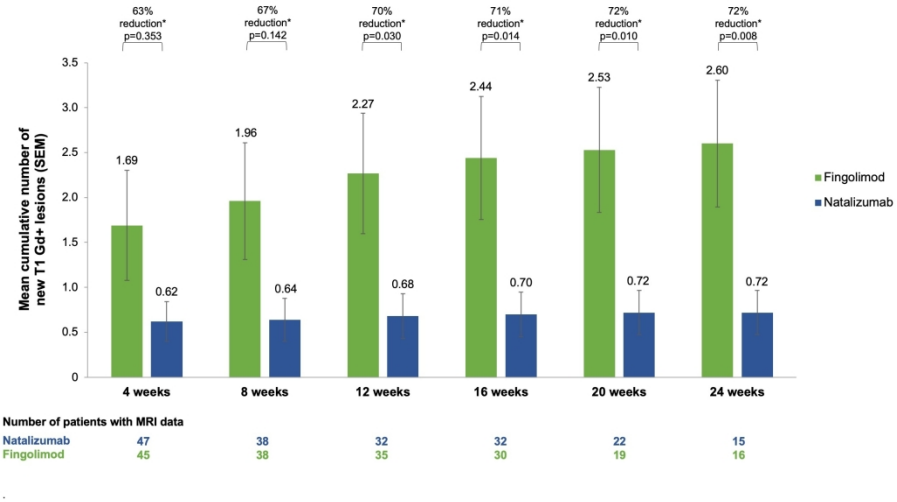
FIGURE LEGENDS

Figure 1 Mean cumulative number of new Gd+ lesions on T1-weighted MRI scans reported over 24 weeks. *Reduction is for natalizumab versus fingolimod. P value is based on a negative binomial regression model adjusted for baseline T1 Gd+ lesion count. Gd+, gadolinium enhancing; SEM, standard error of the mean.

Figure 2 Impact of natalizumab versus fingolimod treatment on relapse outcomes, shown as (A) Kaplan-Meier survival curve of time to relapse over 52 weeks and (B) ARRs before study and on study. *Fingolimod versus natalizumab, based on a Cox model adjusted for number of relapses in the year before baseline, age, baseline EDSS score and years since first symptom. †The x-axis has been truncated at week 36, as no events were observed after week 36. ‡p value is based on a negative binomial model of ARR with treatment as effect, adjusted for number of relapses in the year before baseline, years since first symptom, baseline EDSS score and baseline age. ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale.



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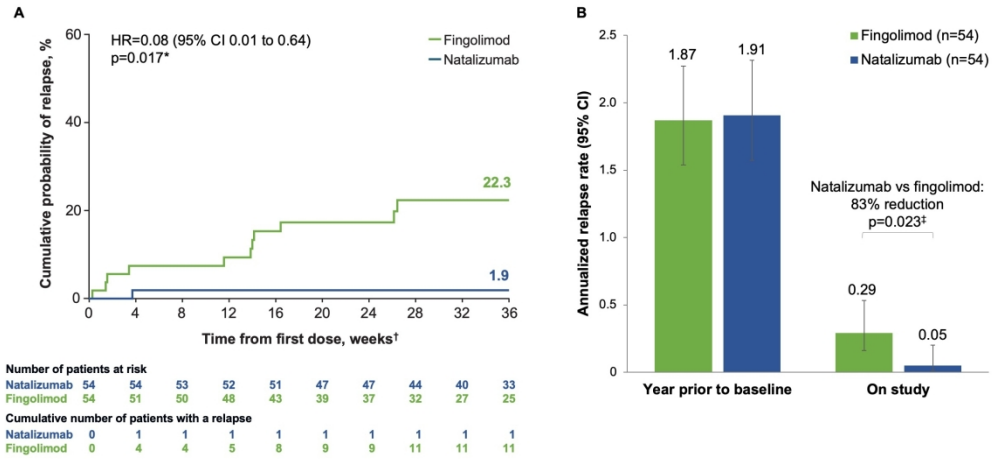

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Online supplementary table 1 Co-investigators

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Jeannette Lechner-Scott	John Hunter Hospital, Australia	Site investigator	Participated in data collection
Helmut Butzkueven	Eastern Health MS Service/Eastern Clinical Research Unit, Australia	Site investigator	Participated in data collection
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Marta Vachova	Neurologicke Oddeleni Nemocnice Teplice, Czech Republic	Site investigator	Participated in data collection
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Jan Mares	Faculty Hospital Olomouc, Czech Republic	Site investigator	Participated in data collection
Olga Zapletalova	Faculty Hospital Ostrava, Czech Republic	Site investigator	Participated in data collection
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Alena Novotna	Hospital of Pardubice, Czech Republic	Site investigator	Participated in data collection
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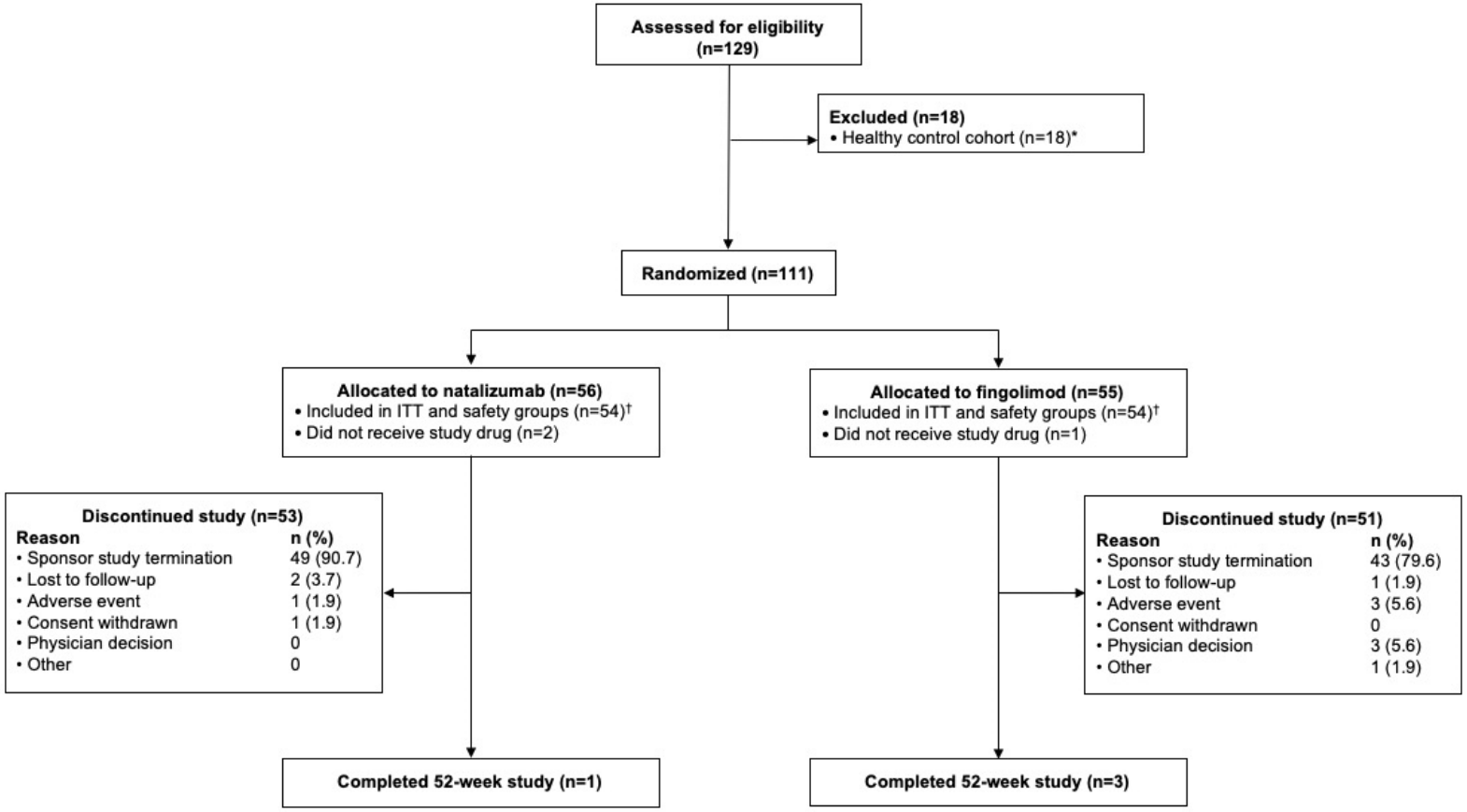
Sibyl Wray	Hope Neurology, Knoxville, TN, USA	Site investigator	Participated in data collection

Online supplementary table 2 Ethics committees

Austin Health Human Research Ethics Committee (RGO)
Azienda Ospedaliera Universitaria Policlinico Umberto I–Università di Roma La Sapienza
Azienda Ospedaliero Universitaria San Martino
Azienda Socio Sanitaria Territoriale Sette Laghi (Presidio Ospedale di Circolo e Fondazione Macchi)
CEIC Autonomico de Andalucia
CEIC Complejo Hospitalario de León
CEIC de Aragón (CEICA)
CEIC de Galicia
CEIC Hospital Universitario Nuestra Señora de la Candelaria
CEIC Hospital Virgen de la Arrixaca
CEIC Islas Baleares
Comitato Etico della Azienda Ospedaliero Universitaria di Cagliari
Comitato Etico dell'Azienda Ospedaliera Universitaria S. Luigi Gonzaga di Orbassano
Comitato Etico dell'IRCCS Centro Neurolesi Bonino Pulejo di Messina
Comitato Etico IRCCS Ospedale S. Raffaele di Milano
Comitato Etico Lazio 1
Comitato Etico Palermo 1
Comitato Etico per le attività biomediche "Carlo Romano"
Copernicus Group IRB
Eastern Health Research and Ethics Committee (RGO)
Eticka komise Fakultni nemocnice Hradec Kralove
Eticka komise Fakultni nemocnice Ostrava
Eticka komise Fakultni nemocnice u sv. Anny v Brne
Eticka komise FN a LF UP Olomouc
Eticka komise Krajska zdravotni a.s.–Nemocnice Teplice o.z.
Eticka komise Pardubicke krajske nemocnice
Eticka komise pri Nemocnici Jihlava
Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice v Motole
Hospital del Mar
Hospital Universitari de Girona Dr Josep Trueta
Hospital Universitari i Politecnic La Fe
Hospital Universitari Vall d'Hebron
Hospital Universitario de La Princesa
Hunter New England Local Health District (RGO)
Melbourne Health Human Research Ethics Committee (RGO)
Mercy Medical Center–DSM
Multicentricka eticka komise Fakultni nemocnice Brno
Rhode Island Hospital IRB
Rush University Medical Center

Seconda Università degli Studi di Napoli
Servizo Galego de Saúde
University of New Mexico HRPO
University of Pennsylvania IRB
University of Sydney (RGO)
University of Texas Southwestern Investigational Review Board
University of Texas Health Science Center at San Antonio Institutional Review Board
Wheaton Franciscan Healthcare IRB
Western Institutional Review Board

Online supplementary figure 1 Patient flow



*Healthy control subjects were screened as part of the diffusion tensor imaging substudy being conducted along with the main study in patients with relapsing-remitting multiple sclerosis. These patients were not treated with natalizumab or fingolimod and were not included in the main study results.
†The safety group comprised all randomised patients who received at least one dose of study drug; the ITT group comprised all randomised patients who received at least one dose of study drug and provided at least one efficacy assessment.
ITT, intent-to-treat.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3–4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5–6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5–6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6–7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7–8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7–8
Sample size	7a	How sample size was determined	6, 8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5–6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13–14
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.